Biopharmaceutics Applications in Drug Development

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To my wife, Bhuvana, my mom, and dad for
their unwavering support and lifelong inspiration
(R.K.)

To my family, Jenny, Alex, and Stephanie for
their understanding, support, and love
(L.Y.)

Preface

Drug product performance is a vital aspect of drug development as it draws on interdisciplinary expertise from both pharmaceutics and pharmacokinetics disciplines. It is at the key interface that the discipline of biopharmaceutics has emerged. The past two decades have witnessed considerable advances in biopharmaceutics particularly with regard to bioavailability and bioequivalence, as they relate to product quality and regulatory standards of approval.

While the foundation for biopharmaceutics has been laid by pioneers in the field and has been captured in early textbooks devoted to this area, a technical gap does exist on the current and emerging applications of regulatory aspects of biopharmaceutics. The current volume presents an integrated view linking pharmaceutics and the biological consequences to drug development decision making. The book is composed of carefully crafted chapters introducing fundamental concepts, methods, and advances in the area of dissolution, absorption, and permeability and their key applications in dosage form performance, with a specific focus on the applications of biopharmaceutical strategies in the development of successful drugs using case studies.

Chapter 1 introduces the basic concepts of biopharmaceutics and discusses the role of biopharmaceutics in various stages of drug development. Chapter 2 describes the molecular and physicochemical properties influencing drug absorption. Chapter 3 examines the utilities and limitations of dissolution testing and discusses biorelevant dissolution methods. Chapter 4 introduces the principles governing drug absorption. It includes all aspects of drug absorption including transport phenomena, factors influencing drug absorption, and methods to evaluate drug absorption. The current industrial practices of evaluating permeability, absorption, and p-glycoprotein interaction are presented in Chap. 5. Chapter 6 investigates the uses of pharmaceutical excipients in drug absorption as enhancers and proposes applications in dosage form design of mucoadhesive materials. Chapter 7 comprehensively describes various transporter families and outlines the role of intestinal transporters in drug absorption. Chapter 8 critically examines bioavailability and bioequivalence from a regulatory perspective, addresses issues inherent in the assessment and demonstration of bioequivalence. The mechanisms and strategies toward BCS are further outlined in Chap. 9. Further, the chapter introduces several case studies encompassing drugs from all BCS classes and multiple formulation types as examples of where a science-based approach to dissolution method characterization has been employed to determine rational product quality testing strategies. Chapter 10 discusses the impact of food in regulatory assessment of bioequivalence and proposes recommendations on the design of appropriate biopharmaceutics studies. Chapters 11 and 12 explore the applications of *in vitro* and *in vivo* correlation (IVIVC) for parenteral (Chap. 11) and orally administered drug products (Chap. 12).

We anticipate that the book will be helpful to individuals who work in the pharmaceutical industry in areas that apply pharmaceutics, biopharmaceutics, and pharmacokinetics, individuals who interact with formulation scientists and pharmacokineticists, as well as those who are in academic and research institutions. Since the fundamentals are also reviewed, we believe that the book will appeal to advanced undergraduate students and graduate students in pharmacy, pharmacology, and allied health professions.

We welcome comments and suggestions for improvement from our readers.

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Introduction to Biopharmaceutics and its Role in Drug Development

Nancy P. Barbour and Robert A. Lipper

1.1 Introduction to Biopharmaceutics

1.1.1 What is Biopharmaceutics?

In the world of drug development, the meaning of the term "biopharmaceutics" often evokes confusion, even among scientists and professionals who work in the field. "Pharmaceutics" narrowly defined is a field of science that involves the preparation, use, or dispensing of medicines (Woolf, 1981). Addition of the prefix "bio," coming from the Greek "bios," relating to living organisms or tissues (Woolf, 1981), expands this field into the science of preparing, using, and administering drugs to living organisms or tissues. Inherent in the concept of biopharmaceutics as discussed here is the interdependence of biological aspects of the living organism (the patient) and the physical–chemical principles that govern the preparation and behavior of the medicinal agent or drug product. This philosophy was pioneered in the mid-twentieth century by the first generation of what we refer to now as biopharmaceutical scientists: those who recognized the importance of absorption, distribution, metabolism, and elimination (ADME) on the clinical performance of medicinal agents as well as the impact of the physical–chemical properties of the materials on their *in vivo* performance. As a result, biopharmaceutics has evolved into a broad-based discipline that encompasses fundamental principles from basic scientific and related disciplines, including chemistry, physiology, physics, statistics, engineering, mathematics, microbiology, enzymology, and cell biology. The biopharmaceutical scientist, therefore, must have sufficient understanding of all of these scientific fields in order to be most effective in a drug development role. A scientist educated in the field of biopharmaceutics or biopharmaceutical sciences could have expertise in a number of interrelated specialty disciplines including formulation, pharmacokinetics (PK), cell-based transport, drug delivery, or physical pharmacy. For the subsequent discussion we will look broadly at the areas of physical pharmacy (pharmaceutics) and PK and their roles and interdependencies in the drug development process.

1.1.2 Physical Pharmacy: Physical–Chemical Principles

Physical pharmacy is a term that came into common use in the pharmacy community in the mid-twentieth century, and the field has grown and evolved over the years. Essentially, physical pharmacy is a collection of basic chemistry concepts that are firmly rooted in thermodynamics and chemical kinetics. Scientists in the mid-twentieth century pioneered research in the areas of physical–chemical properties of drugs and their influence on biological performance (Reinstein and Higuchi, 1958; Higuchi, 1958, 1976; Higuchi *et al.*, 1956, 1958, 1963; Kostenbauder and Higuchi, 1957; Shefter and Higuchi, 1963; Agharkar *et al.*, 1976; Shek *et al.*, 1976). Key aspects of physical–chemical properties discussed in greater detail in Chap. 2, briefly include the following.

1.1.2.1 Solubility

Solubility is a thermodynamic parameter that defines the amount of material (in this case a drug) that can dissolve in a given solvent at equilibrium. Solubility is one of the most critical and commonly studied physical–chemical attributes of drug candidates. The amount of drug in solution as a function of time prior to reaching equilibrium is often referred to as the "kinetic solubility," which can be exploited in pharmaceutical applications to manipulate drug delivery. A compound's solubility impacts its usefulness as a medicinal agent and also influences how a compound is formulated, administered, and absorbed. A thorough review of the scientific fundamentals of solubility theory has been presented previously (Flynn, 1984).

1.1.2.2 Hydrophilicity/Lipophilicity

The partition or distribution coefficient of a drug candidate (log P or log D) is a relative measure of a compound's tendency to partition between hydrophilic and lipophilic solvents and thus indicates the hydrophilic/lipophilic nature of the material. The relative lipophilicity is important with respect to biopharmaceutics since it affects partitioning into biological membranes and therefore influences permeability through membranes as well as binding and distribution into tissues *in vivo* (Ishii *et al.*, 1995; Lipka *et al.*, 1996; Merino *et al.*, 1995).

1.1.2.3 Salt Forms and Polymorphs

Drug substances can often exist in multiple solid-state forms, including salts (for ionizable compounds only), solvates, hydrates, polymorphs, co-crystals or amorphous materials. The solid form of the compound affects the solid-state properties including solubility, dissolution rate, stability, and hygroscopicity, and can also impact drug product manufacturability and clinical performance (Singhal and Curatolo, 2004). There are numerous examples in the literature of the impact of pH and salt form on solubility, and how this phenomenon can be utilized to manipulate the solubility behavior of a drug compound (Li *et al.*, 2005; Agharkar *et al.*, 1976; Morris, 1994). For example, salts can be chosen to impart greater solubility to improve dissolution rate of an active pharmaceutical ingredient (API). Polymorphs and solvated forms of drug candidates can also affect not only the stability and manufacturability of a drug substance but also potentially impact biopharmaceutical performance due to their differing solubilities (Raw and Yu, 2004).

1.1.2.4 Stability

The chemical stability of a drug is important in order to avoid generation of undesirable impurities, which could have pharmacologic activity and/or toxicologic implications, in the drug substance or drug product. Chemical stability of the API in a dosage form influences shelf-life and storage conditions of drug products to minimize generation of undesirable impurities. The pH-stability profile is also important from a physiological perspective considering the range of pH values that a pharmaceutical material may encounter *in vivo*, particularly in the GI tract. Sufficient stability is required for the compound as well during the course of administration. Physical stability refers to changes in the drug substance solid-state form including polymorphic transitions, solvation/desolvation, or salt disproportionation. As mentioned previously, changes in drug substance form can lead to changes in physical properties such as solubility and dissolution rate. At the product (dosage form) level, physical stability refers broadly to mechanical property integrity (hardness, friability, swelling) and potential impact of changes on product performance.

1.1.2.5 Particle and Powder Properties

Bulk properties of a pharmaceutical powder include particle size, density, flow, wettability, and surface area. Some are important from the perspective of a manufacturing process (e.g., density and flow) while others could potentially impact drug product dissolution rate (particle size, wettability, and surface area) without changing equilibrium solubility.

1.1.2.6 Ionization and p*K*a

The ionization constant is a fundamental property of the chemical compound that influences all of the physical–chemical properties discussed above. The presence of an ionizable group (within the physiologically relevant pH range) leads to pH-solubility effects, which can be used to manipulate the physical properties and biological behavior of a drug. For an ionizable compound, the aqueous solubility of the ionized species is typically higher than the unionized due to the greater polarity afforded by the presence of the ionized functional group. The ionizable functional group and the magnitude of the p*K*a determine whether a compound is ionized across the physiological pH range, or if conversion between ionized/nonionized species occurs in the GI tract, and if so, which region. The p*K*a also affects the available choices of counterions for potential salt forms that are suitable from a physical perspective.

1.1.3 Formulation Principles

The goal of a formulation scientist is to manipulate the properties and environment of the API to optimize its delivery to the target tissue by a specific route of administration and to do so in a manner compatible with large-scale product manufacture. Excipients are added to solubilize, stabilize, modify dissolution rate, improve ease of administration (e.g., swallowing or taste-masking), enable manufacturing (e.g., ensure sufficient compactibility to make tablets, improve powder flow in a manufacturing line), control release rate (immediate vs. prolonged vs. enteric), or inhibit precipitation (Gennaro, 1995). The formulation is key to a compound's biopharmaceutical profile since the composition, dosage form type, manufacturing process, and delivery route are intimately linked to pharmacokinetic results. A PK assessment cannot be complete without inclusion of the relevant formulation parameters to establish the appropriate context.

1.1.4 Physiological/Biological Principles

1.1.4.1 Pharmacokinetics

The other broad discipline in biopharmaceutics is PK, which is the study of the time course of ADME (Gibaldi and Perrier, 1982; Rowland and Tozer, 1989). Just as the physical–chemical and formulation principles are intimately linked with the pharmacokinetic profile, the PK profile is directly related to the pharmacologic activity of a drug. For the purpose of this discussion, we will use PK and ADME interchangeably.

Absorption

In most cases, a drug must be absorbed across a biological membrane in order to reach the general circulation and/or elicit a pharmacologic response. Even drugs that are dosed intravenously may need to cross the vascular endothelium to reach the target tissue or distribute into blood cells. Often multiple membranes are encountered as a drug traverses the absorptive layer and diffuses into the blood stream. Transport across these membranes is a complex process, impacted by ionization equilibria, partitioning into and diffusion across a lipophilic membrane and potential interaction with transporter systems (influx and/or efflux).

Membrane transport can occur either passively or actively (Rowland and Tozer, 1989). Passive transport (diffusion) is the movement of molecules from a region of high concentration to one of low concentration. The membrane permeability, which is directly related to the relative lipophilicity of the drug, is a major factor affecting the rate and extent of absorption for a given compound, and for GI absorption the concentration gradient is related to the solubility of the compound in the intestinal brush border microenvironment (Rowland and Tozer, 1989).

Active transport is an energy-consuming process whereby membrane-bound transporters bind and transport materials across membranes, even against a concentration gradient. Physiologically, these active transporters exist to promote absorption of nutrients and hence are typically related to food substances such as peptides, amino acids, carbohydrates, and vitamins. They can lead to absorption efficiency that is significantly greater than what would be predicted based on a passive diffusion mechanism. In recent years many of these transporters have been characterized with respect to structure, cellular location, and substrate specificity (Katsura and Inui, 2003; Sai, 2005). Conversely, active transport mechanisms also exist to transport materials out of cells (efflux pumps). The most well-studied efflux pumps are in the class of ATP-binding cassette (ABC) transporter proteins, including p-glycoprotein (P-gp) and the multidrug resistance protein (MRP) family (Kivisto *et al.*, 2004; Leslie *et al.*, 2005). These natural transporters are cellular defenses that exist to prevent entry of unwanted potentially toxic materials into the systemic circulation, and they can also work against the movement of drug molecules. The reader is referred to Chap. 7, which discusses role of such transporters in absorption processes in detail.

The concepts of permeability, absorption, and bioavailability (BA) are sometimes used interchangeably, while in fact each represents a different aspect related to membrane transport. Permeability refers to the ability of a compound to cross a membrane. A permeable compound may diffuse across the intestinal epithelium only to be actively transported out of the cell. This compound is permeable, yet not absorbed. Likewise, a drug may pass through the intestinal epithelium, indicating absorption, yet be metabolized in the gut wall or the liver prior to reaching the peripheral circulation. This drug is absorbed, yet it is not bioavailable. The relevance of this will be discussed in subsequent Chaps. 4 and 5.

Distribution

Distribution is a measure of the relative concentrations of a drug in different body tissues as a function of time (Rowland and Tozer, 1989) and is related to its ability to diffuse from the blood stream, tissue perfusion, relative lipophilicity, and tissue/plasma protein binding. The apparent volume of distribution (V_d) is reflective of the extent of tissue distribution. Drug distribution *in vivo* is often related to the drug's chemical structure. It can be measured and manipulated during the course of compound optimization by addition or deletion of certain functional groups or structural features. However, formulations typically cannot have significant impact on a drug's distribution properties without chemical alterations such as conjugation or use of specific drug targeting technology.

Metabolism and Elimination

Metabolism is one of the most important mechanisms that the body has for detoxifying and eliminating drugs and other foreign substances. Drugs delivered by the oral route must pass through the liver before reaching the general circulation.

Metabolism at this point is called “first-pass metabolism,” which can limit systemic exposure for drugs despite good absorption. Oxidation, reduction, hydrolysis, and conjugation are the most common metabolic pathways, generally leading to more hydrophilic compounds that can be readily excreted renally. Cytochrome P450 (CYP) enzymes are a family of drug metabolizing enzymes that are responsible for the majority of drugs’ metabolism as well as many drug–drug interactions (Shou *et al.*, 2001; Meyer, 1996). Although the primary role of metabolism is to facilitate elimination of drugs from the body, secondary effects include transformation of drugs into other active or toxic species, which could be desirable in the case of prodrugs (Stella *et al.*, 1985) or undesirable with respect to toxic metabolites (Kalgutkar *et al.*, 2005). The reader is encouraged to refer to authoritative texts in this field.

Elimination of drugs from the body can occur *via* metabolism, excretion (renal, biliary, respiratory), or a combination of both mechanisms. As with distribution, these phases of the drug’s PK profile are inherent to the chemical structure of the drug and are optimized (along with pharmacologic potency and fundamental safety) during the drug discovery process.

1.1.5 Biopharmaceutics: Integration of Physical/Chemical and Biological/Pharmacokinetic Principles and Impact on Clinical Efficacy

In the previous overview discussion, we highlighted some principles governing physical pharmacy, formulation, and PK; the assessment of any one of these is dependent on the context of the others. This interplay is often complex. The integration of these various principles is necessary to define fully the biopharmaceutical profile for a new drug candidate and to evaluate the utility of a particular compound to treat the intended disease. The suitability of any given parameter is always dependent on one or more other, related parameters. For example, the target solubility for a new compound depends on the dose (Curatolo, 1998; Hilgers *et al.*, 2003), which depends on the receptor affinity and BA, which are related to the lipophilicity, which is in turn is related to the solubility. Another common goal is to define compounds with good receptor binding, which is often increased by higher lipophilicity, which can negatively impact absorption and effective dose. Failure to consider all of these factors and their interrelationships can likely lead to the selection of chemical compounds that may not be useful as drugs, or to misleading conclusions regarding interpretation of a clinical issue. Hence, the answer to a question regarding acceptable biopharmaceutical properties is often “it depends.” This point is illustrated in the following general examples of integration of biopharmaceutical principles.

1.1.5.1 Introduction to the Biopharmaceutics Classification System

The biopharmaceutics classification system (BCS) was originally proposed based on the understanding that absorption of drugs in the GI tract *via* passive diffusion is governed primarily by the amount of drug in solution at the luminal–epithelial border and the ability of that drug to diffuse across the intestinal endothelium (Amidon *et al.*, 1995). Flux of a compound is dependent on the diffusivity (permeability) and concentration gradient (solubility). The BCS categorizes solubility and permeability of drugs as either high or low and considers the dose and ionization of the drug in the GI tract. A strict definition of permeability is difficult considering the factors in the GI tract that influence apparent permeability (efflux pumps, metabolism, region), and therefore permeability can be estimated from either *in vitro* transport in cell culture models of intestinal transport or from *in vivo* data on drug absorption. The BCS also recognizes the importance of the dose of a drug, as a high dose drug with low solubility is more likely to exhibit absorption difficulties than a drug with the same solubility and low dose. Conversely, high permeability of a compound may be able to overcome perceived issues with low solubility. Hence, some drugs with extremely low solubility can nevertheless show high systemic BA due to high permeability. The relative balance of these properties influences whether the absorption rate of the drug is controlled primarily by solubility, dissolution rate, or membrane transport.

The BCS can be constructively used to assess the potential for impact of various factors, including formulation variables and physiological changes, on pharmacologic performance. For example, BA of a drug that is highly soluble in the full pH range of the GI tract (BCS Class I or III) would not be expected to be sensitive to formulation factors in an immediate-release dosage form that shows rapid dissolution. Conversely, drugs with low solubility (BCS Class II or IV) have greater potential for effects of particle size, dissolution rate, or excipients on PK behavior. Drugs with low permeability are more likely to show variable absorption, whereas absorption of high permeability drugs could show a dependence on solubility since the rate-limiting step in this scenario is dissolution. The BCS classification of a drug has regulatory implications as well, as current guidances define whether the compound requires additional bioequivalence studies or whether biowaivers may be possible for new strengths or modified formulations (FDA, 2005; Ahr *et al.*, 2000).

The BCS system can also be used by a formulator to provide guidance on the formulation strategy for a new compound. Class I drugs are less likely to require novel drug delivery approaches and have greater potential for equivalence among formulations, whereas Class IV drugs often pose significant challenges to overcome limitations in both solubility and permeability. For the latter, exploration of formulations that include solubilizing agents to enhance microenvironmental solubility or utilization of high energy solid-state forms to affect kinetic solubility could be warranted. Key to all of this is the dose.

1.1.5.2 Impact of Physical/Chemical Properties on Absorption and Transport

The oral absorption process is complex, but for many molecules it can be simplified into a general process that, for a passive diffusion mechanism, requires dissolution followed by partitioning into and transport across the intestinal epithelium. This particular aspect of ADME is most amenable to manipulation by the pharmaceutical scientist to influence PK profile and alter *in vivo* performance for an orally administered drug. Once absorbed, the drug's distribution, metabolism, and elimination are dependent on the chemical structure and physiology.

GI Transit and Ionization

Throughout the GI tract, an ionizable drug can undergo multiple transitions depending on its functional groups and p*K*a values. The state of ionization of an ionizable compound strongly influences passage across membranes as well as solubility. For a compound to be transported efficiently across a biological membrane by a passive transcellular route, the drug must be in solution and non-ionized. These two factors normally work in opposition to each other since non-ionized molecules tend to have greater lipophilicity, which favors membrane partitioning, yet lower solubility relative to ionized species. A weak monoprotic acid with a p*K*a in the range of 4–5 would be non-ionized in the stomach and as such would be at the lower range of its solubility. Once it transits to the small intestine, the drug would be predominantly ionized and have greater solubility. For a weakly basic amine, the ionization state would be reversed, with the drug predominantly ionized and most soluble in the stomach milieu, and non-ionized and less soluble in the small intestine. This might seem to suggest inherent differences in exposure for weak acids vs. bases, but this is not necessarily the case since, as noted previously, solubility is only part of the absorption equation.

Permeability is the other key determinant of exposure following oral dosing. For an ionizable compound, the ionized and non-ionized species both exist in solution, with the relative ratio determined by the pH and p*K*a. As the non-ionized species is absorbed, it is continually "regenerated" as the molecule drives toward a state of equilibrium that is never reached in the dynamic environment of the GI tract.

The dynamic pH environment of the GI tract impacts the utility of salts of ionizable drugs to improve oral absorption. Although a salt form typically has greater aqueous solubility than the corresponding free form, it may not always be the best choice for clinical development. Depending on the p*K*a, pH-solubility factors can lead to variability *in vivo* due to conversion to insoluble salts (e.g., with coadministration of calcium-containing foods), precipitation of insoluble free acids or free bases, or potential drug interactions with concomitantly administered drugs that affect gastric pH (Zhou *et al.*, 2005).

Dissolution and Relationship to BA

Systemic exposure to a drug after oral administration is the culmination of a multistep process that starts with disintegration and dissolution of the dosage form in the stomach contents. Dissolution of a drug *in vivo* is required for intestinal absorption and is impacted by multiple factors, including the solubility of the drug, release rate from the dosage form, and subsequent phase conversions, precipitation, *in situ* salt formation, micellar solubilization in the small intestine by bile salts, and pH gradients.

An integral part of the formulation development cycle is development of analytical test methods to assure quality and integrity of the product intended for human use. Dissolution or drug release *in vitro* in aqueous media under controlled pH conditions, often with added surfactants to solubilize poorly soluble drugs, is a commonly used technique to evaluate oral drug product performance. This *in vitro* dissolution test is relevant as a tool to evaluate the relative performance of different prototype formulations during the formulation development and selection process, and once a product is in clinical testing to assure consistency of the manufacturing process. The development of an appropriate dissolution method should be an iterative process that is done in parallel with the formulation development since choice of dissolution apparatus, media, and other parameters will be dependent on the solubility of the API, the nature of the excipients and dosage form, and the BCS class of the drug. For a method to be useful during formulation development, it should be discriminating, i.e., be able to distinguish differences among formulation and/or process parameters that could impact the choice or *in vivo* performance of the formulation. On the other hand, care should be taken to avoid developing an overly discriminating method that detects differences that are artifactual and/or have no relevance to the use of the product by the patient.

An *in vitro* dissolution test may also be used to assess *in vivo* biopharmaceutical performance if it is physiologically relevant, i.e., is shown to be predictive of *in vivo* behavior. Determining the physiological relevance, however, is difficult with many drugs because of the interplay of multiple factors in a human body that affect drug absorption. The relationship of solubility to absorption in the gut is complex because of the varying composition of the GI fluid and the dynamic environment governing dissolution and absorption. The solubility determined experimentally in a compositionally defined system such as a simple buffer or solvent is a thermodynamic value that reflects the amount of drug in solution at equilibrium (which may take minutes, hours, or days to achieve). In contrast, the GI tract often contains water, fats, pH-modifiers, salts, surfactants, emulsifiers, enzymes, and food components that together determine the effective GI solubility, which may be significantly different from the solubility in an aqueous buffer. This composition also changes with time as the material moves through regions of varying pH (e.g., stomach to small intestine), in a fed or fasted state, and with secretion of pancreatic enzymes and bile salts. Consideration of these additional variables has led to the development of alternative methods to assess solubility and dissolution in biorelevant media such as simulated GI fluids (Nicolaides *et al.*, 1999; Dressman *et al.*, 1998) and to compartmentalized dissolution simulation systems (Parrott and Lave, 2002; Gu *et al.*, 2005).

The only definitive way to establish physiological relevance of *in vitro* dissolution data is to perform a human PK study to correlate dissolution rate using a given method with the resultant PK profile. Ideally, a clear *in vitro–in vivo* correlation (IVIVC) can be made, but in many cases this may be elusive. The BCS class of the drug can be used to predict which compounds could potentially achieve a meaningful IVIVC. Class I and III drugs, because of their high solubility and expected rapid dissolution, would not be expected to show meaningful IVIVCs;

Class IV compounds typically exhibit variable predictability in IVIVCs due to the fact that dissolution and/or permeability could be rate-limiting factors for absorption depending on the particular compound. Class II drugs, however, are most likely to exhibit these relationships since absorption tends to be rapid, leaving dissolution as the rate-controlling step in the process (Amidon *et al.*, 1995; Lennernas and Abrahamsson, 2005; Blume and Schug, 1999). These concepts are elaborated in later chapters.

Maximum Absorbable Dose Concept

A question often raised by scientists designing new drug candidates is "how much is enough?" with respect to solubility and permeability of a compound. In the current climate of drug discovery, key criteria for identification of clinical candidates include potent and selective binding to the target of interest, adequate safety, lack of CYP interactions, and appropriate pharmacokinetic profile to achieve the desired clinical effect. The concept of maximum absorbable dose (MAD), utilizes absorption rate constant, small intestine residence time, intestinal volume, and solubility (Johnson and Swindell, 1996). This concept mathematically illustrates once again the basic tenet of the BCS that passive GI absorption results from the interplay of permeability and solubility. The maximum amount of drug that could be expected to be absorbed based on these two parameters provides guidance as to whether the solubility and permeability are adequate. For example, for a drug with a solubility of 10 μg/mL, the estimated MAD, assuming no limitations due to site-specific absorption, could range from 0.9 mg (low permeability drug) to 90 mg (high permeability drug). Therefore, potent low dose drugs or highly permeable drugs can tolerate what may appear at first glance to be unacceptable solubility.

Impact of Active Transport Mechanisms

Active transport mechanisms are less predictable than passive transport due to the requirement for binding to a cellular membrane ligand. The involvement of active transport systems can lead to erroneous conclusions concerning the permeability of a drug if a passive diffusion mechanism has been assumed. Drug interactions are also possible among drugs that are actively transported, possibly leading to significant changes in pharmacokinetic behavior upon coadministration. Great advancements in the area of active transport mechanisms have been made over the past several years. *In vitro* assays are now frequently used during the early stages of drug development to screen for desirable and undesirable interactions with active transporters, yet more work is required to understand the nature of transporters fundamentally and their ultimate utility in predicting and manipulating PK behavior (Kunta and Sinko, 2004).

1.1.5.3 Strategies to Achieve Target Pharmacokinetic Profile

Although many biopharmaceutical properties are determined by the chemical structure of the compound, there are multiple strategies available for exploiting the properties of any given molecule to try to achieve the desired clinical behavior. The choice of paths to explore is dependent on the nature and extent of the delivery issue to be solved. For example, if poor BA is caused by high first-pass metabolism, delivery *via* a non-oral route may yield sufficient blood levels for activity. Likewise, non-linear PK caused by interactions with active transport systems would not be resolved by improving the dissolution rate of the dosage form.

Route of Delivery

The target PK profile and resultant therapeutic effect (including onset and duration of activity) of any drug are influenced by the route of administration. Oral dosing is normally preferred for a chronically administered medication due to ease of dosing and general patient acceptability. However, compounds limited by solubility, permeability, or first-pass metabolism may not be amenable to the oral route. Delivery alternatives include other transmucosal routes or parenteral administration. Each has its own advantages and limitations. Intravenous administration leads to immediate blood levels and is often used to treat serious acute symptoms such as seizures or strokes. Rapid absorption can also be achieved by non-oral transmucosal routes, including nasal, sublingual, buccal, or inhalation (Chen *et al.*, 2005; Shyu *et al.*, 1993; Song *et al.*, 2004; Berridge *et al.*, 2000). Local treatment *via* ocular, inhalation, nasal, or vaginal routes may be advantageous compared to systemic delivery due to increased potency at the target and decreased systemic toxicity (Rohatagi *et al.*, 1999). In addition, other properties of the molecule may dictate the routes that are possible. For example, protein/peptide drugs are highly susceptible to degradation upon oral administration and are not likely to diffuse across the intestinal barrier unless by a specific active transporter. As a result, these compounds are often dosed parenterally, and more extensive research is being conducted with oral and alternate non-oral routes, including inhalation (Adessi and Soto, 2002). Metabolism can also influence the choice of route of administration. Drugs that undergo high first-pass metabolism may be much more bioavailable by non-oral routes such as rectal, buccal, or nasal (Hao and Heng, 2003; Song, 2004), leading to pharmacologically relevant blood levels that cannot be achieved with oral dosing.

Chemical Modification

An alternative to formulation approaches to modify PK is chemical modification. A prodrug, for example, is a compound that has been designed with a metabolically labile functional group that imparts desired biopharmaceutical characteristics. Prodrugs by themselves are not pharmacologically active but revert *in vivo* to the active moiety through either targeted chemical or enzymatic mechanisms in the general circulation or specific tissue. This type of strategy has been used in many different ways, including modification of physical–chemical properties to improve delivery (Varia and Stella, 1984; Pochopin *et al.*, 1994; Prokai-Tatrai and Prokai, 2003), targeting to a specific enzyme or transporter (Yang *et al.*, 2001; Han and Amidon, 2000; Majumdar *et al.*, 2004), antibody-directed targeting (Jung, 2001),